DR. McNALLY: But then we looked at lower levels and we thought, at lower levels, this is still an okay clinical level for it.

DR. PULIDO: I could see why you chose, what was the reasoning behind the 5 percent. But now have you have a 3 percent incidence with the Acuvue lens and you have a 6 percent incidence with this SEE3. So there is a doubling there. What would happen to that null hypothesis if you used greater than or equal to 4 percent?

DR. McNALLY: I have to say I am not sure.

DR. PULIDO: I would like to know that, though. Did the statistician do that?

DR. SUGAR: Dr. Cutter, why don't you come to the podium. You might be more comfortable.

DR. CUTTER: I doubt it.

DR. SUGAR: You notice that we are interested in your comfort.

DR. CUTTER: I think, in a way, one could do that calculation and the numbers would come out. You take a percent difference and divide it out. I haven't done it. I suspect I know where it is going to come out. You specify the hypothesis for decision-making in advance. You end up making a decision on the basis of the a priori evidence that

you set up for this -- after you have observed the results to kind of go in. I think you are in an estimation procedure.

The absolute difference is less than 3 percent. So I think you have to look at what was observed and maybe put some confidence intervals on the difference and look at the difference for the magnitude and the size of the difference rather than really going back to a hypothesis-testing mode.

I am not trying to be evasive, but I think it has to do with conceptualization. We plan trials with the best information that is available years in advance of when we actually do the analysis. We set up, and we sort of live or die by that proposal.

When you have the data in hand and you can see whether or not your assumptions were correct or whatever, I think it is appropriate to look at the size and the magnitude of the absolute difference or, if you want, proportional difference, whatever you are looking at, and discuss it in those contexts in terms of what size confidence interval you have.

DR. SUGAR: Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Dr. Bandeen Roche. You did mention a confidence interval on the difference in rates. I did a truly back-of-the-envelope calculation. That calculation showed that a 95 percent confidence interval did exclude 0 so that the rates were significantly different. Does this agree with your calculation

DR. CUTTER: Yes.

DR. BANDEEN-ROCHE: Because mine really was back-of-the-envelope.

DR. CUTTER: Yes.

DR. PULIDO: So, again, there is a difference between the rate with the SEE3 and the Acuvue, because, from my quickie thing, too, it looked to me like the confidence intervals had a difference in overlap

DR. CUTTER: Again, not to split hairs, the only other thing I would do is that would be -- you would adjust the p-value for the multiple-hypothesis tests you are doing because the primary hypothesis was a noninferiority test.

DR. McNALLY: If I could add a few comments. When we looked at the unadjusted rates, and, by that, is the number of patients with an endpoint infiltrate divided by the number of

patients dispensed, and when we do the sort of classical comparison of those, we find no statistical difference between the unadjusted rates.

Then, when you perform the life-table analysis to take account of all the patients who discontinued and the other things that happened. Then you come up with these other rates and you get into the discussion you were just getting into.

But, remember, we excluded from that the two peripheral ulcers, so those were two of the more serious of these endpoints, from the control group. This was a conservative thing because one statistically throws us out -- you know, it makes the rate go to 5.7 percent if we included that last endpoint for Acuvue.

We thought, you know, this really isn't representative for Acuvue to go from a 3.3 to a 5.7 because of a statistical foible, I will say, for the life-table analysis. Secondly, we included the second ulcer -- we didn't include the second ulcer at six months. I think if you include those in the analysis, I think that the conclusions then change and you find that there is overlap with 0.

DR. CUTTER: That is correct. And the

foible that Dr. McNally was talking about is since the number of patients who are observed beyond one year, the actual date of their exam starts diminishing, the life-table rate is based upon the event rate in the interval where the event occurs, the number of patients that are still around.

This really makes the rate probably not representative of the control group so we chose to use a conservative -- leaving out those other events. So one could split hairs about whether or not it gets significant or not.

If you include the other events that are known and occurred, but they occurred outside the interval and you are using a life-table estimate for it -- but we have done the analysis looking at if that had occurred at day 365 and what did that do.

DR. MATOBA: This is pertaining to --

DR. PULIDO: It is pertaining -- so, again, you are speculating. There was some speculation that is going on. You had mentioned before, Dr. Cutter, that you could speculate what would happen if the null hypothesis had been changed to greater than or equal to 4 percent. What is your speculation on that?

DR. CUTTER: I haven't done it with all the events included. Again, I think, obviously, someone would want me to include all the events. I don't know who that might be. But I haven't done the calculation where you take all the events and then look at it relative to a 4 percent difference.

DR. PULIDO: You had speculated before? Give me a speculation, p less than 0.05 or not

DR. CUTTER: The absolute difference is slightly over 2 percent. You have got your envelope. The standard error doubles. I think it wouldn't be significant, actually, with 4 percent but, again, if you are including at least one of the two events that are left out.

If you include both events, I am almost certain that they are not.

DR. PULIDO: If you are going to exclude certain events, you also excluded a severe red eye as a problem with the SEE3 lens. Nothing like that ever happened with the Acuvue lens. So what was this severe red eye?

DR. McNALLY: I think I can address your question, contact-lens acute red eye, perhaps, as we explained contact-lens acute red eye. In the contact-lens industry, we tend to put things into

little definitions and boxes which maybe not everybody agrees with. Contact-lens acute red eye is, as defined in our protocol, an acute event involving infiltrates overnight when this occurs and they have pain in the morning and redness and so forth.

The critical part of that definition is that there are infiltrates. However, what happened in the study is that if anybody's eye became injected in an acute way, the investigators often marked acute contact-lens red eye. However, there were no infiltrates and so it really didn't fit that definition.

So we removed that definition but we included them, then. If there were infiltrates, we included them in the endpoint if it met the endpoint criteria. We included them then in the adverse events under infiltrative keratitis if, indeed, there were infiltrates. If all there was was injection overnight, then they were included in the appropriate place which would be, if it was grade 4, it would be biomicroscopy greater than grade 4 in the table.

So they were not excluded. They were in the table under a more descriptive definition of

the findings and symptoms that occurred.

DR. MATOBA: Alice Matoba. The patients who were discontinued for biomicroscopic findings, they were not included in your final analysis; is that correct?

DR. McNALLY: No; all patients were included in the final analysis. The life-table particularly takes into account patients who are discontinued.

DR. MATOBA: So the 3.1 percent versus 5 percent, that first incidence of endpoint infiltrates, that includes those five patients in the SEE3 and the one patient in the Acuvue group who were discontinued and had endpoint infiltrate as a biomicroscopic finding?

DR. McNALLY: It does. That doesn't include the one corneal ulcer that was seen by the ophthalmologist because we didn't have infiltrate data provided, although we had diagnosis of corneal ulcer as well as a scar later. But that wasn't included in that unadjusted 3.1 percent rate.

DR. SUGAR: I have a couple of questions. One, what was your instruction to the investigator concerning infiltrates; that is, were they told to remove the lens, treat them with a specific

medication or do whatever was standard therapy and under what circumstances, if any, were they instructed to culture?

DR. McNALLY: Dr. McNally. I haven't identified myself. It was standard of care was what we were using and so if culturing was felt to be needed by the investigator, then filtering was done.

DR. SUGAR: Do you know what the specific treatment was in terms of medications for the infiltrative keratitises?

DR. McNALLY: We have included a table showing the different treatments. You can refer to the table for the different endpoint infiltrates. This was included in the report. Normally, actually, in the SEE3 there were 9 percent that were just treated by removal and with the control lens, it was a little less than that. I think it was maybe 5, while we are looking for the number.

The rest were either antibiotic steroid combinations or antibiotics, mostly siloxane and this type of antibiotic was used. But we have listed this in the table.

DR. SUGAR: And you also mention a patient who had an adverse response to Tobradex implying

that steroid antibiotic combinations were used in some of these "nonmicrobial keratitises." We don't have a good definition of microbial keratitis industrywide, but it says that some of these patients may, indeed, have had infiltrative keratitis if they were not instructed to culture these patients and they were treated with the steroid antibiotic combination.

DR. McNALLY: Dr. McNally, again. We tried in the report to list everything we could know in terms of how fast they resolved, was there any outcome that was negative for the wearer. We did list, in table 12 on page 58 of 85, the various pharmaceutical agents or other treatment for each of events, the endpoint-event infiltrates that occurred.

DR. SUGAR: Thank you.

Dr. Zadnik?

DR. ZADNIK: Karla Zadnik. You reported that you did not find an association between number of consecutive nights wear before an event; correct. With that small number of events, what statistical power did you have to find that, if it existed? Do you know?

DR. McNALLY: Actually, I don't know if

Gary can answer that one, but we didn't set up the study to test that. So I am not really sure what the power was.

DR. ZADNIK: My concern is that you are saying there is no association and really we are strongly behind that in recommending that language be removed from the product labeling. What I want to know is what power you got to report that there is no association before something as bold as deleting that from the labeling would happen. So I think that is a fairly important number to find out.

DR. SUGAR: Dr. Weissman?

DR. WEISSMAN: You reported one case of Thygeson's and one case of herpes keratitis. Were those patients in which -- I think it was mentioned that the Thygeson's was a second episode for that particular patient. Was there any reason why that patient got into the protocol? Wouldn't they have failed protocol by having had no history of previous eye disease?

DR. McNALLY: We didn't eliminate previous history of eye disease as one of the -- I don't know the word here, but they could get in the study if there was a previous history as long as the

investigator felt that the eyes were quiet and that they were suitable candidates for contact-lens wear.

So it was left to the investigator's decision as to whether they felt this was an appropriate candidate. However, the exclusion criteria -- I thought of the word -- if there was any active corneal inflammation or other things like that at the time of enrollment, they were not able to be enrolled in the study.

But a previous history did not exclude them from participating.

DR. SUGAR: Dr. McMahon?

DR. McMAHON: Tim McMahon. Clarify something for me, Dr. McNally. The postapproval study, the primary endpoint item that will be looked at again will be infiltrative keratitis or it will be infectious keratitis?

DR. McNALLY: The goal is to determine the rate with the proper sample size of infectious keratitis. Because of this problem in terms of is it or isn't it, anything that starts with an infiltrate, the data will be collected and presented and have an independent review board to then determine, by a definition set up in advance

which we haven't done yet because that would be a role of the independent board to say this is the definition, these are the criteria, that will call this a microbial keratitis.

Then we will be able to collect the information. We took infiltrate as an endpoint for collecting data because that is pretty clear when there is an infiltrate. It is just not clear in terms of how you would diagnosis or what you would call that entity.

So that is the entry criterion to collect the data and then that data can be evaluated by the independent board to determine is it a microbial keratitis or is it not.

DR. McMAHON: Then, as follow-up question, as Dr. Holden showed, there seems to be some cumulative risk for microbial keratitis in conventional, nonsilicon hydrogels. Why did you select a follow-up period of only a year?

DR. McNALLY: My first answer to that is that this was the recommendation in the discussions with the FDA.

DR. ROSENTHAL: Could I just make a comment?

DR. SUGAR: Please.

DR. ROSENTHAL: Dr. Rosenthal. We do establish, for the new panel members and for the old panel members, these criteria that they have set up for the clinical trial, often many years before the clinical trial comes to you. So, some of these issues like the hypotheses and so forth are based on the best information at the time.

One of the biggest problems that the agency gets into is when the company decides to change their hypotheses during the course of the clinical trial. I would add that I think that panel should try to accept the hypothesis since it was accepted by us at the time the clinical trial was designed based on the best information available.

DR. SUGAR: Dr. Weiss, Dr. Grimmett. Then I have a question.

DR. WEISS: Dr. Jayne Weiss. I wanted some clarification of the rates of the CLPC. I understand from the data that the patients who had the SEE3 lens versus the Acuvue, the SEE3 category had a much higher rate of having preexistent CLPC. But, if we remove those, then you have a SEE3 incidence of 3.2 percent for CLPC versus 0.9 percent for the Acuvue.

I wanted to find out if you separated out that group and looked at the onset of CLPC, in the total group, you indicated the onset of CLPC was 70 percent within the first three months in SEE3 group versus after three months in the Acuvue group for 75 percent.

In other words, SEE3 had a much earlier onset. But if you take out those who had preexistent CLPC, was there still an earlier onset in the SEE3 group which, to me, might imply that the polymer, itself, would give you a better chance of getting CLPC or were the onsets, then, similar.

I am referring to page 41 of 58 in table 18. I think it is in part 2.

DR. McNALLY: This is Dr. McNally. I don't recollect the answer directly to your question but I think, when we looked at our data overall, we did say that a number of these people had previous CLPC. We don't have enough explanation, perhaps, at this time to say whether, if they did not have that, would they have had a lesser rate.

So we wanted, in our labeling, to say that there is a potential increased risk, particularly if you have had this in the past. We had several

hypotheses in the report, but these are just hypotheses.

One hypothesis was potentially mechanical and that was the timeframe and the drawings that some of the investigators gave as well as some experience we have had from our international trials where, instead of being a generalized capillary conjunctivitis, it was localized in a particular place like you might have seen with the stitches that used to be used, if they still are; I don't know.

But it looked like it was of mechanical origin. Then when you saw when I showed the one fitting where the edge was lifted a little bit off the edge, that the inferior -- and we are thinking, with no proof to bring to you today, but we are thinking that if the lens can lift at the upper part, you might get some irritation up there as well.

But these were hypotheses. We found no correlation with deposits, filming or dirty lenses which is often the other thing blamed for CLPC.

The other difference in the factors is 30 versus 6, and whether that makes a difference, we are unable to answer at this time. So we hoped to

address this in the labeling because we feel this is not a sight-threatening event. It is an irritating event. But we hope to address that in the label.

DR. WEISS: I think it would be, because this is a new polymer which is basically why it can be used under the basis it is, I think it would be interesting and probably easy for the company to look at for the 3.2 percent who had no preexistent condition in the SEE3 versus the 0.9 percent in the Acuvue group to see if the onset was at similar times or much earlier in the SEE3 because, if it is much earlier in the SEE3 group and it is statistically significant, then that would imply that, perhaps, this is going to give you a higher chance of having this condition in these patients. That might need to be indicated in the labeling as well.

DR. SUGAR: Dr. Grimmett?

DR. GRIMMETT: Michael Grimmett. I first just wanted to congratulate the sponsor for a very thorough presentation and detailed booklet brought to panel after the study was completed and not in progress. I thought it was a very nice job.

I have one observation. In prior reviews

that I have participated in, generally speaking, the prescribing range matches the testing range. I just wanted to point out that the testing range for the lens here is +6.00 to -6.00 and the prescribing range is certainly much greater.

I wanted clarification on the exact prescribing range sought because, in different places in the notebook, I was seeing different numbers. In the summary of safety and effectiveness the range is listed from -20.00 to +20.00. In the package insert, it is listed from -20.00 to +10.00 and, in the handout of the slide copies we received today, it is listed as -20.00 to +10.00. What is the exact range the sponsor is seeking?

DR. ROBIRDS: This is Scott Robirds. The approval range that we are seeking is +20.00 to -20.00. That that will be available for dispensing is the +6.00 to -10.00, initially. The approval range would be +20.00 to -20.00.

DR. SUGAR: Can I ask for clarification from the agency? If we approve the lens in a given range, but the guidance is that it can be manufactured and distributed in a broader range; is that correct?

DR. ROSENTHAL: I must say I will have to defer to one of my staff.

DR. SUGAR: Dr. Lepri?

DR. LEPRI: Dr. Lepri. The agency has established a policy over the years, based on their experience and the maturity of the contact-lens technology, that, during the investigation, they do not need to investigate all the available powers.

However, at some point during the approval process, they will have to submit to us the effects of varying thicknesses of the contact lenses in the whole range of contact lenses available to evaluate the safety issue of the oxygen permeability. At that point, the agency makes the determination of the final approval range for the lenses.

DR. SUGAR: Thank you.

Dr. Grimmett.

DR. GRIMMETT: I have two more questions, just of clarification mostly. At one point, it was indicated that about 2 percent, 1.9 percent, of the SEE3 eyes lost two lines or greater wearing the contact lenses. I assume they were correctable with overrefraction or spectacle correction; is that correct?

DR. McNALLY: Dr. McNally here. That is

correct. There was no loss of two lines of acuity in any patient through the study.

DR. GRIMMETT: Just one more housekeeping point. Under adverse device effects, it was listed at one point that a patient had optic neuritis. I am assuming there is no implication that the lens had anything to do with that. It was listed as a matter of all complications seen in all these patients; is that correct?

DR. McNALLY: Dr. McNally. That was in the control group as well and it was listed for completeness.

DR. GRIMMETT: Thank you.

DR. SUGAR: Quick question. You included in your study that patients that were pregnant or lactating could be entered. The draft guidance suggests that those patients be excluded. How many such patients were entered and were there any adverse events in those patients?

DR. McNALLY: As far as reported to us at entry, there were none. Over the course of a year, there were ten subjects in the control group who became pregnant and two in the SEE3 group. So there was a differential there.

DR. SUGAR: So it does have a birth-

control effect. I guess it depends on where you put the lens.

DR. McNALLY: That's right. We will cover that in the labeling. The two in the SEE3 group completed the trial without problem. Of the ten, eight completed the trial, one with an adverse event which was just a grade 3 staining which resolved just with removing the lens. Two of the eight in the control group were discontinued, one because she was confined to bed rest at some point in the pregnancy and the other just because she felt like she didn't want to wear the lenses anymore.

But there were no adverse events of any significance related to that very small group of patients.

DR. SUGAR: Dr. Jurkus?

DR. JURKUS: I had some questions for clarification regarding acuity and poor vision. In your discontinuation rate, you had indicated and you had showed the slide of the defect, but I was still wondering, do you have any information about the number of people who discontinued because of poor acuity who did not have the lens defect.

Second, sort of going along with that, was

there any correlation between poor lens fit and poor acuity? Were they combined in the statistics or were they separated out specifically?

DR. McNALLY: Dr. McNally, again. I don't remember the exact number of fits, how that distributed. It is in one of the tables, but in terms of the rating by the investigators, the vast majority of the fits were rated as optimal. Then, on SEE3, they tended a bit towards the acceptably loose side. We found no correlation with vision in that group.

In those who discontinued for lens fit, I actually didn't look at that data to see if that dropped the vision. We didn't examine every lens that was for a patient who discontinued for lens acuity, but I tried to look at the data in terms of when did it occur. It all did occur in the very beginning, so if you had the first of the lenses you were wearing for 30 days or your second, this was something where you would say, "Well, this is unusual," I wouldn't want to continue.

But if you have cycled through a few lenses and you get one that you can't see with, you say, "Well, let me get another one." So it was all in the first three months that we had these acuity

discontinuations.

Again, there was no loss of best corrected acuity. Most of the ratings, as I showed, I think 98 percent were the same at baseline and 83 percent were 20/20. So there may have been an occasional patient where they didn't get good acuity, but I think it would be no different than any soft contact lens.

DR. SUGAR: Dr. Matoba and then Dr. Bandeen-Roche.

DR. MATOBA: You had a slide in your presentation, Dr. McNally, that was not in the original report and that is the average wearing time for the people in the SEE3 group approached 27 days by twelve months. I wanted to know if that graph was generated from the same tele-diary raw data that was used for the second table which shows that only 67 percent of time were the patients in the SEE3 group wearing their lenses for 20 to 31 days.

DR. McNALLY: This graph was new graph for you, but, because of the questions, I thought I should show it. But it was in the trend analysis profile, table 13. So that is directly taken from there. This was taken from the report and the

case-report forms when, at each visit, they asked what had been your continuous nights in a row that you had worn the lens. That data came from there.

DR. MATOBA: So that is the tele-diary system? It is the same raw data that generated the second table? Is that what you are saying?

DR. McNALLY: No; the second table is from tele-diaries. The first is from the case-report forms.

DR. MATOBA: Okay, because eyeballing the two, they seem disparate to me because they achieved average wearing time of almost 25 days within one month and they stay at that range, 25 to 27. It seems very different from what the tele-diary data reveals.

DR. McNALLY: We looked and we included it. It wasn't included in the panel packet but it was included in the PMA application. We looked at the correlation between case-report form and the tele-diary and they matched very closely.

Then, to maybe address your question here, the tele-diary graph shown there includes all visits. That is the reports for all visits including the first month and the first week and the whole thing where, as you see in the graph

before, the wearing time averages during that first month were lower.

So they do correlate because we looked very closely to see is there a difference in the reporting with the tele-diary versus the case-report form and presented in the PMA packet that they correlate.

DR. SUGAR: Can I, just to understand. If they took the lens out and cleaned it and put it back in, didn't leave it out overnight, that would still shorten their wearing time or --

DR. McNALLY: No; that did not. If they left it out overnight --

DR. SUGAR: If they left it out overnight, it did. Okay.

Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: First, I would like to add my congratulations to sponsor for their study and their presentation. I especially appreciated the matched design and the wide variety of investigators and the really good-faith attempt to provide adequate power. So thank you very much.

I have three questions, one of which is pretty general and the other two are statistical. The general one first may follow up on Dr. Weiss's

comment about this being a new polymer. So, certainly, you cited the decreased dryness symptoms in SEE3 but, in conjunction, there was an increase in burning and tearing and I think lens awareness symptoms.

It just made we wonder whether there could be a subgroup of patients who don't well tolerate the material. I wonder if you could comment on that.

DR. McNALLY: Dr. McNally. There may be a subgroup that doesn't tolerate it. This is why we have stress the first month because we did see -- we were surprised that we had a number of events happening in the first month. We tried to look through the data to come to, what can we find about that. We found a few things. The few things we found, the lens fit. I think these were the discomfort and the awareness, and these things I think are easily explained by the lens fit.

The burning and stinging, I can't explain directly. So there may be some, I think it is like most contact lenses. There are lenses that patients don't like. In this case, we can't say, here is a patient that may not like this lens.

So we really tried to emphasize in the

fitting guides, and if there are suggestions on how to better emphasize, we welcome these -- the first month follow-up time to determine, first of all, are you comfortable with it and are you suitable for a 30-night indication.

DR. BANDEEN-ROCHE: Thank you. And the two statistical questions. The first is that this was a matched design within investigators. So, to my reading, the analyses did not account for the matching or for correlation within investigators in any explicit way; is that right?

DR. McNALLY: Yes.

DR. BANDEEN-ROCHE: So FDA, when it reviews the ultimate materials, I think, should look at analyses that do account for that because it has to do with the believability of the confidence intervals and estimates of incident differences within provider rather than across providers.

The second question has to do with the adverse-event table, all adverse events. I believe you referred to adjusted versus unadjusted. My reading is that those were not life-table estimates. They were just -- I think it is important to provide life-table estimates for those

as well because there was such a difference in the time at risk due to the differential dropout of SEE3 subjects early on.

DR. SUGAR: Dr. Pulido. Then I think we are going to be ready for our break and the FDA's presentation after lunch. Go ahead, Jose.

DR. PULIDO: Following up on Dr. Bandeen-Roche, page 1251, which is product labeling, Package Insert, rather. It has the adverse device effects were reported at the following annual rate. When I add those numbers up, it is 4.63 percent. That is less than the annualized rate estimation for the primary safety endpoint which was 6.1 percent. So did I add up improperly?

DR. ROBIRDS: This is Scott Robirds. What we selected in the labeling were just the corneal inflammatory event. The subset of the table that is one page 12 of 21 in your summary of safety and effectiveness, the very first section, where it is a comprehensive list of adverse device effects.

We elected to focus on just those corneal inflammatory events which totals -- that total that you mentioned. But there were other events, obviously.

DR. PULIDO: But the primary safety

endpoint was infiltrative keratitis; correct?

DR. McNALLY: It was infiltrates grade 3 or greater or with overlying staining.

DR. PULIDO: Right. And you have an annualized rate estimation of 6 percent. So how do you justify saying, later on, that the annual rate is 4.63 percent.

DR. McNALLY: This is Dr. McNally. First, in the proposed labeling, I will make the comment that any recommendations the panel will make in terms of what you include in here, we are very fine with that. These rates here, they don't include -- if you look at them, they don't include the ones that were under serious adverse device effect and perhaps they should have.

But there were a couple of cases in there with anterior-chamber reaction. So we pulled these as a first proposal directly off the table. We didn't include everything in there and we would be very happy to include whichever the panel thinks is important.

DR. SUGAR: Sally has some comments.

MS. THORNTON: I just wanted to let the panel know that the lunches that you have ordered are here. We have reserved room 20G for panel

folks to eat in, and the sponsors, we have reserved room 20H.

We would like to advise everyone to leave the room. We have to clear the room completely during the lunch break for security purposes.

DR. SUGAR: Everyone, please try to be back here by 1 o'clock.

[Whereupon, at 12:05 p.m., the proceedings were recessed to reconvene, at 1:00 p.m., this same day.]

AFTERNOON PROCEEDINGS

[1:05 p.m.]

DR. SUGAR: We will now proceed with the FDA presentation on PMA P010019.

FDA Presentation

DR. SAVIOLA: Thank you, Dr. Sugar. At this time, I will introduce Myra Smith who is a microbiologist in our branch and the project leader for this review group. Any additional comments I will reserve until after we present the questions, if you have any questions for us.

MS. SMITH: I am Myra Smith. The primary panel reviewers for this PMA were Dr. Matoba and Dr. Jurkus. The FDA team responsible for review of this PMA included Dr. Bernard Lepri, clinical review, Dr. Gene Hilmantel, statistical review, Dr. Daniel Brown, toxicology review, Dr. Jimmy Chen, chemistry review and myself for the microbiology review.

Dr. Lepri will now present the clinical issues.

DR. LEPRI: Good afternoon, members of the panel, sponsors and other guests.

[Slide.]

I am about to present to you just some key

elements upon which I believe your review and recommendations should focus regarding this device for the SEE3 Focus contact lens.

[Slide.]

The history of extended-wear contact lenses is one of low patient satisfaction, unfavorable rates of complications and higher risks of complications.

[Slide.]

The primary complication of concern, both historically and here today is that of corneal ulcers. The relationship of hypoxia and the development of complications, namely infiltrates and ulcer development, is well known as reflected in this slide.

[Slide.]

The sponsor believes that the development of the SEE3 lens, lotrafilcon A, addresses these issues. Lotrafilcon A is a very high Dk lens. The Dk of SEE3 is 140. The characteristics of their device and the sponsor's presentation emphasizes the role of oxygen permeability in its performance.

[Slide.]

The range of power of lenses studied in this investigation were from -6.00 to +6.00

diopters with a mean of -3.05. In the next slide, one can see that there is a notable difference in the range of lens powers tested in the clinical trial as compared to the ranges available by the sponsor.

[Slide.]

Unlike other refractive devices whose ranges of affectedness are limited to those studied, FDA has established policy over the years to deal with this technical discrepancy. This policy addresses the issue of the safety with respect to lens thickness and higher powers as related to oxygen permeability.

[Slide.]

This has been established by FDA based upon the maturity of contact-lens technology and FDA's experience in dealing with this issue. FDA determines the appropriate range of power approval for extended-wear lenses based upon the effects of lens thickness on lens permeability. The sponsor will have to demonstrate these data to FDA before final approval.

[Slide.]

In order to achieve their goal of marketing the SEE3 lens for 30-day extended wear,

the sponsor, in communication with FDA, designed a prospective, randomized open-label clinical trial for a determination of noninferiority to the control device.

A note I would like to add is that, in conversations and communication with the company, in the preparation of this IDE several years ago, the wide range of rates reported in the literature were what contributed to their selection of the 8.6 percent infiltrate rate to use as a benchmark for targeting a sample size that would yield sufficient number of patients to provide some reasonable assurance of safety and effectiveness when combined with the postapproval study. So it was the attempt to not have an overly burdensome investigation and yet not have one that produced so few patients that we had absolutely no confidence in the data.

[Slide.]

Based upon the reported Acuvue infiltrate of 8.6 percent as reported in the literature, this surrogate endpoint was selected utilizing the criteria presented in this slide.

[Slide.]

This surrogate endpoint was chosen because of its effects upon sample size and due to the fact

that most infiltrates are not infectious. Infiltrate development usually precedes ulcer development. This endpoint would provide an estimate of safety upon which a postapproval study would be conducted to attempt to determine the true rate of microbial keratitis for this device.

[Slide.]

The design was based upon an enrollment number and endpoints determined by a per-patient perspective. 697 test patients were enrolled and this translates to an enrollment of 1,394 eyes for SEE3 which provided reasonable sampling to achieve an estimate of the rate of infiltrates.

[Slide.]

It is unreasonable to speculate that everyone who is fit with extended-wear lenses could or should wear them for 30 days. Special consideration was given to this fact in the design of this study. It was intended that this study would determine the proportion of patients that could safely wear this type of contact lens for 30 days. The endpoints in the study were tailored according to this consideration.

[Slide.]

I am now going to present to you some key

clinical-trial observations that FDA believes should be taken into consideration in your recommendations regarding the SEE3 30-day extended-wear lens.

[Slide.]

One interesting observation in this study was that an infiltrate event in one eye carries a six-times greater risk of a second event in the same or fellow eye as compared to having a first event.

[Slide.]

Another finding is that SEE3 infiltrate endpoints occurred earlier in the study than did Acuvue endpoints. Standard contact-lens labeling generally states that the incidence of ulcers increases with the length of wear time. FDA requests that the panel's discussion of labeling will address whether this general warning about ulcers regarding wear time should be kept in the labeling or should labeling reflect the findings of this specific study for SEE3.

[Slide.]

42.4 percent of the 33 SEE3 subjects who developed infiltrate endpoints experienced them at one month whereas only 23.8 percent of the Acuvue

subjects did at this time. From the second month on, the number of endpoint events was similar in number and timing of occurrence with 19 occurring for SEE3 and 16 for Acuvue.

[Slide.]

For subjects that experienced more than one endpoint event, which were 10 in number for SEE3 and 4 for Acuvue, 70 percent of SEE3 subjects experienced the endpoint in the first month as compared to 25 percent for Acuvue. This can be inferred to mean that SEE3 events occur early on in wear when patients are most closely monitored.

[Slide.]

The study results also revealed that there were no differences in gender or age for infiltrates. For this study, infiltrates were not restricted to daily wear or new lens wearers. 9 out of 13, or 69.23 percent of SEE3 and 100 percent of the 9 Acuvue subjects who experience infiltrates had worn extended-wear lenses on a 7-day basis prior to participation in this study.

[Slide.]

Adverse events as related to wear time are a major issue in the evaluation of extended-wear contact lenses. The average wear time in this

study for all completed patients was 27 days at 12 months. This was achieved by 67.2 percent of the dispensed cohort who had completed the study. Even 28.9 percent of discontinued patients wore the lenses for an average of 27 days.

[Slide.]

Of the discontinued patients, only 2.4 percent were discontinued for positive biomicroscopy findings. The majority were discontinued for lens-fit discomfort and acuity followed by lost-to-follow-up. All of these issues have been addressed in the sponsor's presentation this morning.

[Slide.]

Some of the most important aspects of a clinical trial are those that occur between scheduled visits. In order to attempt to obtain some of this information, the sponsor included a patient-managed daily diary in this investigation. Review of this information by the sponsor revealed that SEE3 patients had fewer complaints of dryness than the Acuvue patients. 19.8 percent of SEE3, as compared to 24.2 percent of Acuvue patients, reported dryness.

[Slide.]

Statistical analyses of these subjective reports were found to be significant by the sponsor. The sponsor proposes that the labeling claim that SEE3 lenses reduce dryness symptoms associated to wearing hydrogel lenses. The panel should address the issue of this finding and its clinical significance in the labeling discussion here today.

[Slide.]

Question No. 1: do the data presented in PMA P010019 provide reasonable assurance of safety and effectiveness for the proposed indication for use?

[Slide.]

This is the indication statement concerning the first two issues which we believe are the focus of this PMA discussion today regarding the general indication for refractive conditions and length of wear.

[Slide.]

Question No. 2: does the panel recommend any modification of the proposed wording of the indication statement?

[Slide.]

Question No. 3: please discuss the merits

of including the maximum 30-day time period in the indication statement. Does the panel recommend that it be included in other sections of the product labeling rather than the indication section?

[Slide.]

Question No. 4: does the panel have any specific recommendations for the proposed product labeling in terms of warnings, precautions, clinical data outcomes or practitioner-directed or patient-directed labeling?

[Slide.]

Question No. 5: does the panel recommend that the sponsor conduct a prospective postapproval study within the U.S. population to gather information on the incidence of microbial keratitis?

[Slide.]

Following that question is No. 6 in topic and in number: in consideration of the potential differences in the standard of care and device-usage patterns outside of the United States, does the panel have any recommendation concerning the use of foreign data in the postapproval study?

Thank you for your time.

DR. SUGAR: Thank you. Does that end the FDA presentation or do you have more?

DR. LEPRI: That is pretty much it.

DR. SUGAR: Are there questions for FDA? Jose?

DR. PULIDO: Jose Pulido. Dr. Lepri, again, as I try to resolve in my mind what is my biggest concern, knowing what I had discussed this morning, do you feel that there is a 1.5-fold or greater risk of infiltrative keratitis for this lens versus a 7-day-wear lens?

DR. LEPRI: The data show that the rates are definitely higher than they are for 7-day lenses. But then, again, that was expected. In fact, at the panel meeting when we discussed these issues last November, Dr. Hilmantel's presentation was asking the panel to conjecture on what X amount of fold increase would the panel find acceptable for marketing a new 30-day lens.

Those numbers that were recommended by the panel were much higher, 2, 3 and 4 times, when he presented those data. This is actually much lower than I would have expected to see. But it is definitely higher than 7-day. It stands to reason. The longer you wear it, the longer the cornea is

stressed.

I would like to make one more comment that I forgot to make.

DR. SUGAR: Go ahead.

DR. LEPRI: That was to thank and commend the sponsors for providing me with a very concise, succinct and fluent document to review and for their extreme cooperation and helpfulness in working through this entire process in the past five years that I have been with FDA.

DR. SUGAR: Thank you. Are there other questions for FDA? If not, the sponsor, if they so choose, can make comments. We have ten minutes for that. Do you wish to retake the floor? Seeing no desire, we will then proceed -- I think we will reserve the right to question both the agency and the sponsor if the need arises in our deliberations.

We will now move on to the deliberations.

Committee Deliberations

DR. SUGAR: We are going to begin with the primary reviews, the first of which is Dr. Jurkus.

DR. JURKUS: This is Jan Jurkus, the primary reviewer. I would like to start out my review by saying thank you very much to Dr. Lepri

and Dr. Hilmantel for their excellent, excellent reviews that were given to me and also to Ciba for a very readable and sort of straightforward report.

Much of my review has been already talked about so I will try to make it brief in terms of the highlights. Things that I find to be of major interest in this report include the lens material, itself, this being a lens that has a transmissibility of 175 times 10^{-9} in the -3.00 power. This certainly, as a high oxygen-transmissible lens, does, indeed, exceed the criteria that was set forth by Holden and Mertz of '87 as well as the more current criteria proposed by Lehood of 125.

So the actual oxygen transmission is something that I think, as a practitioner, we certainly look forward to. In reviewing the study, itself, some things that I found of interest, starting with the number of lenses that were not dispensed in terms of the trial lenses. There were 39 subjects who did not get lenses dispensed to them as part of the study.

Well over -- or actually about 50 percent were due to the inadequate fit. So, changing or adding an additional base curve would, at least in

theory, take care of 50 percent of the people that were unable to have this lens prescribed for them.

In the number that had been discontinued, again, poor vision, discomfort and lens fit made up the majority of the reasons for the lens to be discontinued. There, too, the statement that the sponsor makes that a flat fit with the SEE3 may also result in small amounts of edge lift, that may be judged better by subjective reports of lens awareness or discomfort than biomicroscopy findings is one that is very interesting and I think needs to be highlighted very carefully in the practitioner manual.

In the past, as practitioners, we were always looking to fit the loosest lens that was stable on the eye where here the loosest lens may, indeed, not be the most appropriate for a particular patient or a particular group of patients. I think that should be certainly addressed in the labeling portion of the practitioner guide.

When it comes to the safety endpoints, I agree with Dr. Hilmantel's assessment that it can be concluded that the SEE3 lens is not inferior within a tolerance of 0.05 to the Acuvue lens with

regard to the primary safety endpoint of corneal infiltrates with staining or grade 3 infiltrates.

The timing, again as illustrated in all of the reviews thus far, was something that I did find to be very interesting and, again, should be indicated very much in labeling that the infiltrate existence was much sooner with the SEE3 than with the control lens. I think that should certainly be highlighted and stressed to practitioners.

When it comes to the percentages of serious significant adverse events, nonsignificant adverse events, the study did show that they were really remarkably similar between the SEE3 and the Acuvue lenses.

The thing that did stand out, as commented earlier, was the development of CLPC, the contact-lens-induced papillary conjunctivitis. This is something that I think practitioners, again, need to be made very much aware because GPC as a whole, or CLPC, had been sort of dwindling in clinical practice and now this may be a resurgence to be checking for, although the incidence rate of 4.6 percent certainly did fall within the percentages for extended wear that are included in the literature. Those that I could find were between 2

and 16 percent.

So it wasn't outrageous but, certainly, within the portions that are currently available.

When it comes to subjective symptoms, the report of dryness was 19.8 for the SEE3 group and 24.2 for the control group. Although statistically that has been shown to be significant, when you think of it in clinical terms, it sort of breaks down to, with the SEE3 group, one out of five people is going to tell you that they experienced dryness. With the Acuvue, one out of four people is going to tell you that they experienced dryness.

From a clinical standpoint, when you are in a busy practice, that one-person difference doesn't seem to make a huge influence on a apractitioner's selection of choice. So I still have a hard time with the statement that they had proposed for labeling regarding dryness.

When it comes to the visual outcome, I was very pleased that the 98.1 percent of the test group maintained acuity within two lines of dispensing as well as the efficacy outcome that 95.5 were able to wear to lenses for 22 to 31 days.

So I guess, to sort of summarize my review of this, when I looked at the whole thing, putting

it in very simplistic terms, what I was hoping this document would answer would be two things; one is does the lens work and, secondly, does the lens do any harm.

To answer those two specific questions, I can say that the answer to, does the lens work, does it do what they say it is going to do, I would have to say the answer to that has shown to be yes, that people certainly can see with this lens on and that it does provide extended-wear capabilities.

The vision measurement to be 20/20 was achieved by 83 percent of the subjects while maintaining Snelling contact-lens acuity within two lines of dispensing was achieved by 98.1 percent. This I thought was a very remarkable and very laudatory achievement.

Continuing with that answer, can people wear this contact lens on an extended-wear basis for up to 30 days, again, the numbers were a little bit confusing between the 67 percent and the 95 percent, but I would certainly say that it is safe up to about that 30-day for most people.

Looking at the second question, does this do any harm, for that part, we are not really sure. At this point, the study had showed that there was

no significant harm done and that the 5 percent endpoint infiltrate rate does not seem to be totally different than what is currently available.

I do believe very strongly that the postmarket surveillance study will give us a much better answer to that particular question.

So, at this point, in my opinion -- I am not supposed to give my opinion yet, until we have completely discussed this?

DR. SUGAR: You may.

DR. JURKUS: I can give my opinion? Okay. In my opinion, I think labeling certainly can address some of the issues that we have discussed but this has been shown to be a safe and effective lens.

DR. SUGAR: Thank you.

Dr. Matoba?

DR. MATOBA: Thank you. I just had a few relatively minor points. Since many of the points actually pertain directly to the questions, I thought maybe I would just go down and discuss each of the questions that the FDA has posed.

The first question was do the data presented in PMA P010019 provide reasonable assurance of safety and effectiveness for the

proposed indications for use. Initially, I was troubled by the fact that only 67 percent of subjects in the SEE3 study had worn the lenses for the 22 to 31-day period whereas 92 percent of subjects in the Acuvue study had worn the lenses for the 5 to 7-day period. So for a basis of comparing the incidence of the endpoint infiltrates, it seemed to me that they really have not compared 7-day wear versus 30-day wear and yet wanted approval for 30-day wear.

On the other hand, based on the data presented today looked at it another way, the average wearing time goes up to 25 days and approaches 28 to 27 days by the end of the 12-month period. I am no longer as bothered by that discrepancy. In terms of other questions I had regarding the nature of the infiltrates that were seen in patients who were discontinued from the study, the sponsor has addressed my questions from the initial review.

So my answer to No. 1 would be yes.

For 2, would I recommend any modifications in the proposed wording of the indications statement, I still have a problem with the dryness symptom as an indication for use of this

potentially 30-day extended-wear lens.

If a practitioner were to look at that indication only and then not go down to look at contraindications, it may be construed as recommending that a patient with potentially aqueous-tear deficiency and related ocular-surface disease may be an appropriate patient for dispensing of the 30-day lens. I would be very concerned about that possibility.

So rewording of this indication or some other modification, as the sponsor has already indicated they may be willing to consider, would be appropriate, I think.

In terms of the third question, I had no problem with the maximum 30-day indication in the statement.

In terms of the fourth question, proposed labeling changes, I think that the fact that this lens did have a statistically significant increased incidence of GPC in their study patients should be included and sponsor has already indicated that they would include that in the labeling.

The second thing I would like to suggest is that labeling include the fact that once a patient has had one infiltrate, they are at greatly

increased risk for a second infiltrate. So the practitioner should use extra caution in monitoring those patients who have had at least one infiltrate.

In terms of the fifth question, does that panel recommend that the sponsor conduct a prospective postapproval study, I would. The sponsor has already indicated that they have plans to proceed with that study.

The sixth question was are there any special considerations for the study outside the U.S. My answer would be no.

DR. SUGAR: Go ahead Ralph.

DR. ROSENTHAL: Dr. Rosenthal. Could I just make two comments about the questions. I don't know whether you want me to make them now or whether you want me to make them before you start to discuss them specifically.

DR. SUGAR: I think it is fine. Go ahead.

DR. ROSENTHAL: Thank you. I think I am getting this right. Jim, correct me if I am not.

DR. SAVIOLA: I am listening carefully.

DR. ROSENTHAL: In the past, we have not prepared patient-directed labeling with contact lenses. Question 4 specifically asks should we

require the company to prepare patient-directed labeling as opposed to just practitioner-directed labeling.

DR. SUGAR: Could you define that for us? What does patient-directed labeling mean?

DR. ROSENTHAL: As with other devices, the patient-information booklets have to be made up by the company and provided to the practitioner who dispenses the lenses. Sorry; that would be if they were required.

So Dr. Matoba just brushed by that question rather quickly and I want to be sure you discuss that issue because I think that brings up the second issue is that we really -- if a company is proposing a 30-day approval study and, of course, we are agreeing that it should be included as a condition of approval, there are still questions out there about the safety of the lens over a 30-day period.

The past has shown that, long before I came to the FDA, lenses were approved for a certain period of time and then, because of problems out in practice, they had to reign in the time of approval. I am not sure you are all aware of that. I wasn't in this country when it all happened, but

apparently it happened in the '80's.

So there have been issues in the office about whether or not the incidence should include the 30 days when we may, in fact, have to reign it in after a postapproval study. That is why we specifically asked about that issue, if the postapproval study shows a very incidence of microbial keratitis.

DR. SUGAR: Could I ask what our options are? If we feel that this is demonstrated safe and effective for 30-day use but there is a concern about the postapproval study, what middle ground do we have to approve the lens but reserve the option which you always have, of course, to change the indications in the future.

DR. ROSENTHAL: Correct. Dr. Saviola will be happy to answer that for you.

DR. SAVIOLA: Let me take a step back first before I answer that direct question. What Ralph is alluding to is a couple of points. On Question 4 regarding panel-specific recommendations for labeling and patient-directed labeling, one of the things, as you brought up, the patient booklets are passed out to the different doctor offices by the different account managers, detail people,

whoever.

They are not necessarily always passed out to the patient. So the thought is, is there some other vehicle that people should perhaps get risk information about this device and, along those lines, the traditional ones, as Ralph described, with the package insert that is directed to the practitioner, the practitioner fitting guide and the patient information booklet, what we normally have seen, but the concept, perhaps, of a patient package insert might be something that you want to think about or talk about in the context of your discussion similar to what you have seen often in different pharmaceutical advertisement, the back page of an ad will have the patient package insert, essentially, which has some information in it that talks about the fundamental information that is found in the regular package insert which is warnings, precautions, contraindications, et cetera, but not using technical terms or technical terminology to that degree. That was the first thing.

The second thing Ralph was talking about was the idea that while the proposed indication has lots of different elements in it, wear time being

one of them, the idea that -- and this is, again, in the context of our questions that we posed to you for discussion, the idea that the wearing period, or the recommended wearing period, may or may not have to be part of that specific indication.

As it is proposed now, it is written up to 30 days as recommended by your eye-care practitioner. Well, that second part, as recommended by your practitioner sort of gets forgotten and it becomes a 30-day lens.

So in the context of a failed postapproval study where the rate is significantly higher, if we were to have to make an adjustment later on in the maximum wearing period, the indication, if it just said for correction of refractive error would remain the same, and the modification would occur in a different part of the labeling, such as prescribing information, wearing time, what have you.

So, in essence, our questions are getting to the discussion of your clinical viewpoints, pros and cons of having the maximum 30-day period in the indications statement as opposed to some other part of the labeling such as prescribing information.

DR. SUGAR: Dr. Pulido?

DR. ROBIRDS: Jose Pulido. I don't understand. You are saying that, fine, comes out the postapproval study and it shows there may be an increased risk and you want to back off a little bit, so you have to change it down in your scheme of things, down where it says length of time, but it wouldn't be in the indications.

The way it is set up now, you would just change it in the indications, so what is the difference?

DR. SAVIOLA: The other element that is --

DR. ROSENTHAL: Let me just clarify something. It is not our scheme of things. We are asking the panel's recommendation. So we have not proposed either. The company has proposed an indication statement including a 30-day lens. We have just raised the specter of another possibility.

DR. PULIDO: The question, still, is what's this difference.

DR. SAVIOLA: Far be it for us to lead you in your determinations. We were asked to bring the idea to you for your comments and, during the course of the discussion, perhaps alternatives.

While we do know that there is reasonable assurance of safety and effectiveness up to 30 days in the population that has been studied, we know from experience that these preapproval studies don't translate into the general population.

So the true incidence of microbial keratitis in the general population really hasn't been studied or established. Having gone down this road before, we have some experience here so, in the internal discussions in the office, there is a mix of opinions one of which is that there might be some merit in not including the length of wear time specifically in the indication statement because, A, that might push people to wear it as a 30-day lens and forget the second part, "as directed by your eye-care practitioner."

Two, because we don't really have the full picture -- we have a preliminary picture at this point in time and we know from experience that the preliminary picture didn't translate to the general population.

DR. SUGAR: Dr. Matoba?

DR. MATOBA: Alice Matoba. It seems to me, whether it is in the indication or not, if it is anywhere in the labeling or the advertising, it

is going to be considered 30-day lens no matter where you put it. My question is, actually, I was surprised that you allowed data from the patients who hadn't worn the lenses for 30 days to be included in your study.

If you had problems before, why would you not have told the sponsor up front that they would have to design a study that would strictly compare 7-day versus 30-day wear?

DR. SAVIOLA: The initial brilliant idea we had in how to deal with these devices the second time around was to allow subjects in the study to wear the lens for whatever period of time that they would tolerate so we would have a distribution of 7-day, 14-day, 21 to 30-day, a strata of outcomes to get some sense for how often people could really tolerate this lens because, again, our sense is going to be that not everybody is going to wear this lens for a month.

That idea didn't really pan out because, in the course of the study, they ramped everybody up to 30 days. So, it didn't really disturb us much that there were people who completed the study in less than 30 days because that was sort of one of our original expectations of the outcomes, that

there be a natural demarkation of people who could tolerate different periods of wear.

We are seeing here that that really played out. So, to say you must have a 30-day wear period of be discontinued from study wasn't really consistent with the way we were trying to get some information about how this would translate into the total population.

DR. SUGAR: Dr. Zadnik? I'm sorry; Alice. Did you have a follow up to that?

DR. MATOBA: No.

DR. SUGAR: Dr. Zadnik?

DR. ZADNIK: I am not sure I understand who the postapproval study that is proposed is going to resolve any of this. If you enroll 2,000 people for a year and this lens at 30 days, or 20 days, or however long the people end up wearing it or the practitioners recommend it is just as good as or bad as our experience has been so far, you are going to get 4; right?

Does that mean we are going to be sitting here and saying, well, we got 6, so it is a lot worse. Is it going to have to be that we got 40 so it is a lot worse? Or we got 2, so it is a lot better? Or we got none out of those 2,000 people

in a year so it is a ton better?

You know, I realize there has to be a limited scope to that to make it even feasible, but I am not sure doing something of a limited scope for the sake of doing it if it is not going to really answer the study question -- that is, is the annualized microbial-keratitis rate greater than 20 per 10,000 in Focus Night and Day wearers, I don't get the point of the postmarket study other than us --

DR. SAVIOLA: You are correct that, at that scope, it won't answer the question. We ask the questions to you for discussion purposes of your opinions about a postapproval study. We did not want to get into a whole discussion of the specifics of that simply because it would get really convoluted very quickly.

We had a discussion of this at our November meeting last fall and got some sense for it. We have already had discussions with the firm. We had discussions with the industry in general. There are some considerations in terms of how much it is going to cost companies to do these studies.

We are not going to be satisfied with 2,000 people.

DR. ZADNIK: I just want to --

DR. ROSENTHAL: Excuse me, Dr. Zadnik. This is Dr. Rosenthal. This is proposed by the company.

DR. ZADNIK: I understand.

DR. ROSENTHAL: This has not been agreed to by the agency.

DR. ZADNIK: I just want to sort of enter a cautionary note that if, as we have these discussions, we fall back in, "It's okay; there is this postmarket study and some of these questions will be answered." I am just not sure in my head I could design a feasible study that would answer some of these questions until this lens is out in the hands of practitioners.

DR. SAVIOLA: Right. Our initial goal was a 10,000 to 15,000-patient study which is significantly expensive to conduct. It will be somewhere between 10,000 and 2,000 as an initial study. Then, depending on the outcomes, we go from there. If it is something that shows consistent with the preapproval data, then we are all set. If it is something that shows it is questionable, maybe there is need for additional studies after the first one. Who knows?

But, as it is presented to you in this context, this is the company's initial offer, so to speak.

DR. SUGAR: The answer to question 6 has an impact on that, also, in terms of what other data they can recruit for dealing with the question.

Did you have something else you wanted to say, Jim? What we will do is have a little bit more of this general discussion and then we will go specifically question through question.

Sally wants to know if you want to sit down, Jim.

DR. SAVIOLA: Unless you have any other questions, I will sit down.

DR. SUGAR: She is very interested in everybody's comfort today. That is nice to see.

Dr. Weissman?

DR. WEISSMAN: This is Weissman. I had a question specifically about the indication for aphakic use. As far as I know, none of the subjects in the initial study were aphakic and many of us who have seen aphakic patients have a bias that aphakic patients may have a higher rate of infection.

So the question I have is why is that on the table?

DR. SUGAR: I think we can ask the sponsor to make a brief comment on that.

DR. McNALLY: This is John McNally with Ciba Vision. That we did not, indeed, study in aphakic patients. The labeling, that is the standard labeling for most contact-lens approvals. So we did not study it. We think it might be an interesting thing to study and proceed with, but we put that in because that is the standard labeling for contact lenses. That is very much open for discussion.

DR. WEISSMAN: It might be impossible to do because there are not many adult aphaks running around. I just wondered why it was there. It might be something that the agency might want to consider.

DR. SUGAR: It may be something that we may want to, at the end, with -- a change in the labeling.

Dr. Bandeen-Roche? She is just agreeing. Okay. Other general comments? Dr. Zadnik?

DR. ZADNIK: Dr. Karla Zadnik. Dr. Matoba, you mentioned, I think, the papillary

conjunctivitis sort of label warning kind of thing. One of the problems I see in this dataset for making that kind of statement, that either this lens is riskier in terms of that developing or less so, is that the randomization didn't work for a previous history of giant papillary conjunctivitis.

There are a lot more patients in the SEE3 group than in the Acuvue group who had a previous history of contact-lens papillary conjunctivitis, I think. Isn't that what the data say? So I think that to then say this lens is at increased risk, I think is impossibly confounded, perhaps, by that historical risk factor.

DR. MATOBA: Alice Matoba. I think you might say something like, "in the study, a greater incidence of GPC was found."

DR. ZADNIK: Could it say something, that, specifically in people who had a previous history of or could it mention -- in other words, if you are a previous GPC sufferer, this might not be the lens for you.

DR. MATOBA: That would be fine. But I don't think you can just throw it out because you found a way to explain it, because that is the study that was done and that is what it showed.

DR. ZADNIK: I think you want to advise patients who should and who should not try this lens

DR. MATOBA: Yes; that would be fine.

DR. ZADNIK: Maybe that is who shouldn't try it.

DR. MATOBA: Right.

DR. SUGAR: Go ahead, Dr. Weiss?

DR. WEISS: Jayne Weiss. That was the comment that I was addressing my question to the sponsor before is that when they separated out those patients who had not had previous GPC, and I will call it GPC because it is just so much easier for me, they had an approximately 3 percent rate in the SEE3 category of GPC in those who did not have a previous history of this, but a 0.9 percent in the Acuvue.

I don't know if that is statistically significant and the sponsor evidently didn't have that data. I don't know if the onset was earlier. So it is a question that I think the sponsor should go back and answer. I don't know if and how we should address that particular thing in the labeling.

DR. ROSENTHAL: Rosenthal. May I just say

that it is obvious that it is important and if you tell us you would like it to be addressed in the labeling, based upon the comments that you have put forward, we will insure that the company does the appropriate analysis to insure that the labeling reflects the various issues.

DR. SUGAR: At this point, I would like to organize our discussion around the six questions that the agency presented us with, and begin with the first question. Dr. Matoba, do you want to -- you have already, but go ahead and just make a --

DR. ROSENTHAL: Excuse me; Rosenthal. Could you take the first question last because, essentially, it is what you are going to be asked to vote upon. So I would rather you -- well, you can do as you wish.

DR. SUGAR: I am not sure that that is the case. I think that we can deal with the issue and then deal with the details. That is what the subsequent questions are.

Go ahead, Alice. Just restate your stance on the question.

DR. MATOBA: All right. Alice Matoba. I am going to restate my stance on the question.

DR. SUGAR: Thank you.

DR. MATOBA: Word for word?

DR. SUGAR: Any way you want.

DR. MATOBA: Initially, I was bothered by the fact that only 67 percent of the subjects in the SEE3 group wore their lenses for 22 to 31 days whereas 92 percent of the subjects in the Acuvue group wore the lenses for 5 to 7 days, the upper range of the wearing time.

So it seemed to me that there was a bias, possibly due to this discrepancy. But, subsequently, sponsor did show other data indicating that the average wearing time went up to 25 days within 1 month and approached 27, 28 days over the next 11 months.

So I believe that there was a fair comparison of approximately 30-day wearing time versus 5 to 7 days for the Acuvue group. The incidence of the endpoint infiltrates, the surrogate for a microbial keratitis, was lower than expected and is an acceptably low range for both groups.

Other concerns I had regarding the nature of the peripheral ulcerations and infiltrates in the subjects who were discontinued for biomicroscopic findings were addressed by the

sponsor. So, at this time, I feel that there has been provided reasonable assurance of safety and effectiveness for the proposed indications for use.

DR. SUGAR: Is there anyone who feels otherwise and would like to discuss it? Please. Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: I am Dr. Bandeen Roche. I am not saying that I feel otherwise, but I did want to make just a couple of statements about my view of the data. So I have to rely on my panel associates' judgment to some degree, their clinical judgment.

The first issue is how good of a surrogate are corneal infiltrates for the outcome that we ultimately care about, microbial keratitis. I would be very interested to see what the corneal infiltrate rate at the grade that has been defined in this study was in the old time extended-wear studies because it would be a real cautionary tale if the rates were similar and yet things ultimately didn't turn out well.

Secondly, I would like to reiterate Dr. Pulido's concerns about noninferiority, the tolerance chosen. It is not unreasonable but, to some extent, it is arbitrary. I think that Dr.

Matoba did highlight the more important thing which is what is the rate, is it acceptable rather than does it fall within a 5 percent tolerance.

The adverse-event rates are likely understated in the SEE3 group because a life-table analysis was not used to develop those rates and the record was such an appreciably higher early drop out in the SEE3 group than in the Acuvue group, so this is something that should be taken into account in evaluating whether those rates are acceptable or not.

I am talking about the other adverse-even rates at this point, and then what other we decide, I just feel that it is important that patients understand what we mean by safety and effectiveness, including the sorts of outcomes that this study has not established and was not intended to establish.

DR. SUGAR: Other comments? Thank you for those wise comments. I am not supposed to make judgments, but -- okay. We are not going to vote on the answers to these questions, but we are getting a sense of the panel for the agency's sake.

The next, and I think important, issue is do we recommend any modification of the proposed

wording of the indication statement. Janice, do you want to comment on changes --

DR. JURKUS: In the proposed wording, one of the -- or, actually, there were a couple of things that were not included that I would like to have included in the indication statement. In the alternative practices and procedures section, I think it would be important that we include the use of daily-wear contact lenses and also a different alternative to this would be refractive surgery LASIK.

DR. SUGAR: Is that for the indication for the labeling? I think that is more a labeling issue.

DR. JURKUS: That is more a labeling issue. Okay. Then, in the indications statements, as stated right up here --

DR. MATOBA: That is not the whole indications statement, is it?

DR. JURKUS: Yes; that is what was in the book.

DR. WEISS: It is on page 1348 of 1314 of the sponsor's manual, if you are looking for it. There are two statements that are missing from that on the screen.

DR. ZADNIK: Karla Zadnik. I think the one that Dr. Jurkus mentioned in her comments was on this expanded version of it. It is the dryness issue.

DR. JURKUS: Right. Dr. Jan Jurkus, again. The indications for use where they do have dryness symptoms, that the Night and Day contact lens may reduce dryness symptoms that are present with regular hydrogen soft contact lenses. I object to that. I think it should be eliminated. They did not truly study what I would consider to be regular hydrogel contact lenses. They looked at one specific type and there are many other types that had not had any indications for study.

So, at this point, I would exclude that statement.

DR. SUGAR: Are there other agreements, disagreements? I agree. Jayne?

DR. WEISS: Jayne Weiss. I would agree with that. I also think Dr. Weissman's comment was an important one is that the lens was not studied in aphakic patients. So I am not sure that should be included as an indication, although I think perhaps, later on in the labeling, we can address the fact that it may be useful in aphakic patients

although it was not studied. I feel a little uncomfortable saying it is indicated for aphakic persons when there wasn't one patient in the study who was aphakic.

DR. SUGAR: Dr. Yaross?

DR. YAROSS: In the context of that, if that is, in fact, what is referred to as the class labeling indication, typically, if something is an across-the-board indication for a class, industry looks to see if there is a specific reason to exclude a specific product from the class.

So I think the question there is is there some special reason to believe that this product is specifically inappropriate to aphaks. You might want to consider that as part of this class indication issue because I would expect that many of the other products that carry this indication also have not been specifically studied in aphaks.

DR. SUGAR: Dr. McMahon?

DR. McMAHON: Actually, responding to that issue, Dr. Weissman is correct in that there is past data with the older form of hydrogels and extended wear did show a higher complication rate in the aphakic population, particularly in the vantage groups. There has been no evidence to

controvert that with this particular material, so I would support considering removing aphakic. The next question would be about pseudophakia. I am less worried about that, in addition to the dryness issue.

DR. PULIDO: Just a question. How is diabetes taken care of in the contraindications. They have any systemic disease which may be exacerbated by or interferes with contact-lens wear. Then, they have before that, corneal episthesia.

Do we need to worry about the effects of diabetes on corneal surface and the ability to use these lenses? Was that even evaluated? I am a retina person, so I am just asking the panel.

DR. WEISS: Jayne Weiss. They have, soon after that, a contraindication, with any systemic disease which may be exacerbated or interferes with contact-lens wear. I think that would be fairly global to go through various conditions that could cause, let's say, decreased immunity or increased sensitivity of infection.

We can go through -- there are multiple diseases, aside from diabetes. But I think they have good will in terms of trying to indicate that

there may be other diseases that a practitioner might want to consider not using the lens.

DR. SUGAR: Let's stay with the indications. Dr. Weissman?

DR. WEISSMAN: This is Weissman. I agree with Dr. Weiss that there are an awful lot other immune diseases. I think covering with a global statement is appropriate. In the aphakia think, I want to make it plain that I don't consider, necessarily, this lens to be a problem for aphakic patients, that aphakic patients often have a lot of comorbidities that is what maybe has caused the problem in the past. But the data was while not absolutely convincing, given the old statistics and the few numbers, quite compelling at the time that aphaks did run into an awful lot more trouble attempting extended wear than phakiks did.

DR. SUGAR: Go ahead, Dr. Jurkus.

DR. JURKUS: Jan Jurkus. One of the reasons, from my understanding that most of the aphaks did have more difficulty, could have also been with the oxygen transmission through the older types of lenses where, indeed, this lens, having a much higher oxygen transmission, may actually benefit that aphakic population as opposed to

saying that we shouldn't use it for them.

DR. WEISSMAN: I don't disagree, Jan, but I think that needs to be shown and then the indication added. That is what I would like to see, if you can find enough aphaks to study. That is other thing.

DR. SUGAR: Dr. Weiss?

DR. WEISS: Jayne Weiss. I would pose this question to Dr. Saviola in terms of the lens studies coming through here, what percentage have indicated that the lens is used for, or can be used for, aphakia when no aphakic patients have been included in the study. If, as you are commenting, most of the studies have not included aphakic patients but have included aphakia as an indication, then we shouldn't have any higher requirements for this sponsor than anyone else.

DR. SAVIOLA: As you saw in the sponsor's presentation, they are only making the lens in low-plus powers. In the protocols that we have seen, there have been a limited power range of people who were enrolled. The historical perspective, from our standpoint -- Dr. Lepri gave you some information about how we look at power ranges and permeabilities and things like that based on lens

thickness.

We have applied that, certainly in daily wear, across the plus, minus-20 power range. If you can do a +12.00 to +20.00, it should be for a aphakic population. Even though it is really hard to find new aphaks, there are certainly aphaks out there who need different contact lenses. Other than rigid lenses, those get harder and harder to find in the soft-lens arena.

For this particular device, the thing to consider is that they want to stay up to 30 days. If you feel strongly as a panel that, in an aphakic population, there are some different considerations, you might be fine with this up to 7 days for aphakic wear but if, up to 30 days, you have reservations, well then we should hear about that.

Generally speaking, though, we apply the permeability analysis and decide how high they can go based on safe levels of oxygen.

DR. WEISS: So just as a follow up, does the FDA have any concerns that a +10.00 lens or a +15.00 lens would have any higher -- just because of the lens makeup, have any higher risk than a +5.00 lens.

DR. SAVIOLA: I would have to see their thickness analysis and look at the difference in permeability before I could answer that question.

DR. WEISS: It sounds like, from the clinician's standpoint and the FDA standpoint, it is a big question as to whether this is as safe in aphakia.

DR. SAVIOLA: Again, in light of a 140 Dk material compared to materials out there that are in 18 and 28 Dks that are currently approved for extended wear, they are going to have a pretty thick lens in order to raise some transmissibility concerns with us.

DR. SUGAR: Dr. Weissman and then I would like to --

DR. WEISSMAN: I don't mean to monopolize it, but, as a clinician, I would like to see this lens available particularly for aphakic infants. But I just think that possibly a different wording at some point in the labeling might be appropriate.

DR. SUGAR: So is it correct that the sense of the panel is that the word "aphakia" should be removed from the first indication. Is there agreement by head nodding or something? We are not allowed to vote on this. Jayne?

DR. WEISS: Jayne Weiss. I am reluctant to remove it but I would like to indicate that the study that was performed was not performed on aphakic patients. I wouldn't want to make it such that a clinician could not use this for an aphakic patient because of our stringent criteria in the indications statement. I would like to give the clinician some leeway at the same time as indicating that we don't have any data.

DR. SUGAR: Ralph is bristling there.

DR. ROSENTHAL: Rosenthal. A clinician in the practice of medicine can use an approved device as they see fit if there is nothing in the -- you know, unless there is something in the labeling that warns them they better not use it. Then, of course, even then they can still use it as the practice of medicine.

So whether it is in the indications statement or not does preclude whether or not a physician or an eye-care practitioner can use a lens in a certain population. So it is just not in the indications statement. It is a regulatory issue.

DR. WEISS: Jayne Weiss, again. Clinicians from legal aspects may be a little bit

more reluctant when it is not included in the indications.

DR. SUGAR: The sense that I am getting is that we want to remove the word "aphakic" from this but add to the labeling a statement that information on the performance of this lens in aphakia is not yet available, or something to that effect; is that correct, or am I misstating it?

Go ahead, Jose.

DR. PULIDO: Jose Pulido. After hearing this discussion, I feel, in my mind, at least, that for me I would feel more comfortable leaving the aphakic there and then, later on in the warnings section, put, "the study did not involve patients that were aphakic so the results in these patients should be looked at very carefully," something to that effect.

Does that satisfy Dr. Weissman and Dr. Weiss?

DR. WEISS: Jayne Weiss. I would agree with Jose's recommendation.

DR. SUGAR: And Dr. Grimmett? There are enough nods that I think we can proceed. Are there other modifications of the proposed wording for the indications statement? One was, then, to eliminate

the fourth bullet which is Focus Night and Day lenses may reduce dryness symptoms that are present with regular hydrogen soft contact lenses.

That was what Dr. Jurkus proposed. The issue is -- I think the issue is, one, does this imply that the lens is indicated more for dry-eye patients. The other is, is this just a statement that this lens performed better than another lens.

In the earlier discussion, the issue came up that we are talking about the Acuvue lens, not all hydrogel soft contact lenses. So one modification would be to make it specific. The other would be to eliminate this and have it in the discussion in the labeling. The other would be to just eliminate this. I think those are the options.

Would someone like to champion one of those?

DR. EDRINGTON: This is Edrington. I would recommend eliminating the statement.

DR. SUGAR: Are there those who feel otherwise? Dr. Grimmett?

DR. GRIMMETT: I would agree with that because it may be statistically significant, but I don't think it is clinically relevant. So I agree.

DR. SUGAR: So the sense of the panel is that we would eliminate that fourth bullet.

The other indication, the lenses may be prescribed for daily wear or extended wear for up to 30 nights of continuous wear as recommended by the eye-care professional. I guess that that gets discussed in our third question. Anything else on the second question? The third question is really still dealing with the indications; that is, does the panel recommend that the 30-day statement be included in only other sections of the product labeling rather than the indications statement, with the agency discussing the option of removing the 30 days from the indication and putting it elsewhere in the labeling, assuming that we require a package insert to be presented to the patient receiving the lens.

Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. I just want to point out that, at least by my review, I did see the statement in the package insert, tab 8, part 7, in the professional fitting guide, tab 9, part 7 and in the patient booklet, tab 10, part 7. So, as it stands now, at least as per my review, I saw the statement at least in four locations. So it seems

like it is all over the place.

DR. SUGAR: I think that the issue that the agency has is with it being up front in the indications statement and perhaps being a marketing issue that this is marketed as indicated for 30-day wear, for wear up to 30 days. This is for us to discuss.

Karla?

DR. ZADNIK: Karla Zadnik. I guess I would ask Dr. Saviola would the alternative be to make the second bullet say, "the lenses may be prescribed for daily or extended wear as recommended by the eye-care practitioner," because then they could be 60 days, or 120 days, or years?

DR. SAVIOLA: That is the other side of the coin; yes. It is an extended-wear lens and the doctor decides. In the other parts of the labeling, as Dr. Grimmett said, the 30-day wear period still remains in those sections of the labeling. It is just not in the indications section.

DR. ZADNIK: Or would you recommend an alternative that said, "for up to 7 nights of continuous wear?" I mean, I am trying to get sort of if you reject this, what is the alternative

option.

DR. ROSENTHAL: Excuse me. Really, though, that is for you. If you reject this, that is for the panel to recommend. Please.

DR. SAVIOLA: I am not going to recommend to you what you should do.

DR. ZADNIK: Okay.

DR. SAVIOLA: But, again, the reason this came up and the time period in the indications, if you say to us, "we don't think it should be an indication but it should be as it stands now in the other parts of the labeling," well, yes; it still could be promoted and sold and whatever as a 30-day lens. But still, technically it is not indicated for that.

We had a rate number before for the hydrogels based on epidemiological data that got published. And we said, "That is too high a rate number. We can't live with that rate number, 30." Everything went back to 7 days.

Okay; we don't have the rate number now so that is part of the problem with saying, "Yes; we can go with 30," because we have a missing piece of the puzzle which you won't have until later on.

Again, it is up to you to discuss the pros

and cons of the idea that someone would run it up to 2 or 3 months certainly is an issue. If you feel like that is a strong enough issue to say, "You guys work out the regulatory details. We think it should be 30 days," well, then, say that to us.

DR. SUGAR: This is presented -- we are reviewing this a 30-day lens. To eliminate it from the indications, I think, is game-playing and really eliminates the basic issue. So I, personally -- am I not supposed to say "I, personally," anything?

I am supposed to vote in ties, but I personally think that we ought to leave it in.

Go ahead, Mike.

DR. GRIMMETT: Mike Grimmett. My belief would be to leave it in the indications statement as well as in the other sections that I already mentioned, the reason being that, for all practical aspects, the manufacturer-sponsor would still advertise it up to 30 days. I don't see the difference in practical terms to the clinician if you somehow hide it out of the indications statement.

The sponsor did do a study up to 30 days.

So I would leave it in the indications statement.

DR. SUGAR: Is there anyone that feels otherwise? Do you want to comment, Janice?

DR. JURKUS: Just a possible consideration. We could change that, instead of up to 30 days to include use of the lens from 1 to 30 days. That way, people would not get the idea that you have to use it for 30 days. It can be used 1, 2, 3, 4, 5, you know, any number of days at a time.

DR. SUGAR: I am not sure that "up to" says anything different than that.

Jayne?

DR. WEISS: Jayne Weiss. It is almost as if there is an elephant in the room and we just want to ignore the fact that the elephant is sitting next to us.

DR. SUGAR: That is not Mike that you are talking about.

DR. GRIMMETT: I have lost some weight recently.

DR. ROSENTHAL: So have I.

DR. WEISS: Diplomacy has never been my strong suit, as you can tell.

The sponsor did an excellent study to show that this can be used in many patients successfully

up to 30 days. Let's give them credit for that. Let's put it in the indications. If postmarket shows something else, then we will change it.

DR. SUGAR: Other comments? We will move on to Question 4; does the panel have any specific recommendations for the proposed product labeling in terms of warnings, precautions, clinical data, outcomes or practitioner-directed or patient-directed labeling?

Dr. Saviola specifically pointed out the option of patient-directed labeling which -- I need to understand this. People, when they get contact lenses now, do not have a package insert with the lens? Is that correct?

DR. ROSENTHAL: This is Rosenthal. Have you seen the advertisements that are published in papers?

DR. SUGAR: Sure; on the back of the page, they have listed the --

DR. ROSENTHAL: Ad infinitum, all the issues. I think that is a patient-directed advertisement. So, up to now, there has not been that type of requirement.

DR. SUGAR: For contact lenses.

DR. ROSENTHAL: For contact lenses.

DR. SUGAR: But there is a requirement that a package insert be given or not?

DR. ROSENTHAL: Oh, yes; of course a package insert is included in all --

DR. YAROSS: A package insert and advertising issues are really quite distinct. One falls under the restricted device regulation and that is distinct from labeling that is disseminated to the practitioner to then distribute to the patient.

I guess the question is does any other contact lens at this time have patient brochures that are provided to the practitioner to provide to the patient.

DR. ROSENTHAL: There is, apparently, a patient brochure required -- not required --

DR. SUGAR: But is not in the package. When you open the box of your Acuvue lens, it is not there.

DR. ROSENTHAL: It is not in the package. It is required, but I understand for many years, it is sort of made up but no one ever uses it.

DR. YAROSS: Sponsors do have no control over what the practitioners do in that respect.

DR. ROSENTHAL: That's correct.

DR. SUGAR: But if it was required to be in the box, this would be dispensed, I presume, in clusters of six lenses or whatever. Then we could request that.

DR. SAVIOLA: Let me just, again, recap. For current lenses, as the sponsor described before, there is labeling guidance out there. It talks about a package insert that is directed to the practitioner with information to review with the patient. There is a practitioner fitting guide and there is also a patient information booklet.

Those are all elements of labeling that we review as part of the approval for either daily or extended-wear lenses.

The words "patient-directed labeling" that we put into the question bring up to idea, do you think there should be something else besides those three elements currently, such as a patient-directed package insert.

Whether or not that patient-directed package insert gets printed on the back of an advertisement is a restriction issue and that is something that we don't need to discuss within the context of panel because we make the decision whether or not we are going to restrict it under

502(q) and (r). So don't get the two confused. We are basically saying, do you think -- and, of course, we have contact-lens consultants and panel members so they are quite familiar with the labeling that is out there, hopefully, that you have seen it.

Do you think, in the context of this thing, a new class of lens device, that there should be something else besides what is currently out there.

DR. SUGAR: We are going to have to break up this discussion into how we are going to change the labeling and then what we are going to do with the labeling.

Go ahead, Dr. McMahon.

DR. McMAHON: Tim McMahon. Currently, we have extended-wear lenses that are approved out there already for 7 days. We don't require corporations to provide this patient-specific instructions, if you will.

This proposal is being held, basically, to a comparison to those already approved lens designs. I don't feel that we need to add an additional burden to them after we have already pretty much come to a pretty close consensus that

they have adhered to that.

So I don't see the rationale, despite the fact that this is a new class of lenses at this point, to add that patient-specific label.

DR. SUGAR: Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: I may be misunderstanding, but I have to respectfully disagree. I do feel that there should be patient-directed labeling. Again, maybe I am just misunderstanding semantics, but I think the patient absolutely must receive certain information given the history of continuous-wear lenses, that there has been an unfortunate history with them.

We have a promising new product before us, but I do think that patients absolutely need to see the data in some understandable form that we have seen here today and they also need to understand that the ultimate endpoint has yet to be evaluated. At least, that is my opinion.

DR. SUGAR: Dr. Pulido?

DR. PULIDO: I think that intraocular lenses are extended wear also. Patients don't receive -- do they receive? They don't receive a patient --

DR. SUGAR: The physician, with the

package with the intraocular lens, receives the intraocular lens and the package insert that details the indications, the contraindications.

DR. PULIDO: But nothing for the patient. It is the doctors --

DR. SUGAR: The doctor chooses to either give it to the patient or not give it to the patient.

DR. PULIDO: So it is the doctor's responsibility to let the patient know of the adverse events, et cetera. I think that there is nothing more extended wear than an intraocular lens and there is nothing special done in that situation.

DR. SUGAR: Dr. Edrington?

DR. EDRINGTON: Edrington. Intraocular lenses, I assume there is informed consent where the majority of extended-wear patients are not having informed consent.

DR. SUGAR: Dr. Zadnik?

DR. ZADNIK: Karla Zadnik. I really think this patient education has to happen when the patient initially starts with these lenses. That, almost by definition, has to come from the doctor as it should with all other extended-wear products

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that are already approved.

Remember, these patients are going to start getting six packs or two packs or something of these and they are going to have that same monster patient-directed labeling inside every one for them to pitch over their shoulder because they are on their third year of wear and they are on their sixth box of lenses.

So I think for the education to be meaningful and for the communication to do what it is supposed to do, it really has to come from the practitioner and be directed in that way rather than directed at the patient each and every time.

DR. SUGAR: Although we cannot control that.

DR. ZADNIK: Of course not.

DR. SUGAR: Dr. Bandeen-Roche, and then Dr. Jurkus.

DR. BANDEEN-ROCHE: That would just be my question. That sounds absolutely right but how do we insure that it happens. I guess the answer is that we can't.

DR. JURKUS: Jan Jurkus. It seems that the thing that we are looking for is to try to protect the patient, to let the patient know that

not everything is absolutely perfect with this type of lens or could not be absolutely perfect.

So something to consider might be, on the package, on the box that it comes with, giving the patient directions on what to do if they have any signs of irritation, redness, change in vision or lens discomfort, "Take out the lens and see your practitioner."

If we put that on every box that the patient gets, hopefully, it would prevent the more serious complication from happening and it is something that the patient might actually read instead of little tiny pieces of paper that they would throw out.

DR. SUGAR: Dr. Pulido.

DR. PULIDO: Jose Pulido. On page 1247, it says, the first thing after it says package insert, Focus Night and Day extended-wear soft contact lenses, prescription only. So, whenever you give a prescription to a patient, you always tell them -- I mean, you are legally bound to tell them the risks and benefits.

Whenever I prescribe Timoptic, I don't give them the package insert of the risks and benefits of the Timoptic. It is my duty to have

already told them that. So we are making this much different than we are doing anything else that comes by prescription only.

DR. SUGAR: Dr. Weiss?

DR. WEISS: Jayne Weiss. Just to play a little bit of devil's advocate, I agree with Dr. Pulido that we shouldn't make the rules and regulations for this any more stringent than anything else we do and that would be unfair. But, in my own practice, I see more and more patients ordering lenses by phone or mail and maybe never even interacting with an eye-care professional.

In that sense, is this lens going to be a higher risk than the other lens and maybe we should have a different set of criteria. I don't have an answer for that. I am just throwing that out.

DR. ZADNIK: But they are not ordering this different modality of lenses the first time they get them from Lens Express and Linda Carter; right? They can't get these the first time, I am assuming.

DR. PULIDO: It is prescription only.

DR. ZADNIK: It is by prescription so they have got to have a prescription for this type of lens initially. That is where the education from

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the doc comes in and then only when they get their replacement lenses through and 800 number would they not be receiving this additional labeling.

But I think Jan's idea of something that really gets the message across; "if your eyes hurt or you can't see, take your lens out and call your eye doctor." That is really what you want the message to be. Why not have the sponsor think about delivering it in a way that the patient might actually see it.

DR. SUGAR: Is that within our purview to suggest that to the agency? Ralph?

DR. ROSENTHAL: The panel may suggest whatever they like, Dr. Sugar.

DR. SUGAR: I think we are suggesting that. Is that the sense that there is not strong support for patient-directed labeling but there is support for a warning label on the package that states, "this is prescription only." It already says that on the package, I think, for all lenses, for all soft lenses, and that in the event of pain, redness, discharge, you should seek attention from an eye-care practitioner.

Dr. McMahon?

DR. McMAHON: I think it is a good idea

but I have some qualms about specifically directing this particular sponsor with this particular product only doing this. This should be something that goes across the spectrum which I don't know is within the purview of this panel.

I have this sort of grumbling feeling that this is being somewhat unfair.

[Many panel members in agreement.]

DR. JURKUS: Jan Jurkus. I happen to disagree. We are looking at a totally new modality that could possibly have more patient noncompliance. We are giving our stamp of approval to something that is different than what is already out there. So I would think that, from whatever we have from this point forward, if it falls into the same grouping, should have pretty much the same requirements.

But this is different than anything else that we currently have on the market.

DR. SUGAR: What I guess I would like to do is straw poll the panel in terms of how many feel that there should be special specific package labeling as we just described; that is, the warning labeling on the package. All those who would like to suggest that that be done, signify by raising

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your hand.

[Show of hands.]

DR. SUGAR: There are four. Again, I am not counting and we are not voting. Those who would not like to see that done?

[Show of hands.]

DR. SUGAR: Six. So you have a sense that that issue was raised but there is not overwhelming support for it.

Go ahead, Dr. Edrington.

DR. EDRINGTON: I would just like to add, what Karla said about the way patients access lenses these days. We are starting, in a sense, a new modality. In the '80's, when we ran into extended-wear problems, the practitioner was primarily the one delivering the lenses to patients.

So, I think when you look at those two things together, I think the extra labeling is not a bad idea.

DR. SUGAR: Dr. McMahon, we are going to move from this into the specific wording of the labeling.

DR. McMAHON: Tim McMahon. That straw vote should be recognized as that is pertaining

just to this. I think it would be interesting to know how the panel feels about adding that particular type of warning to all lenses.

DR. SUGAR: Because airplanes leave at 7:00 tonight and earlier for some people, I would like to leave it with the issue at hand and not get more global. But if someone wants to usurp my ability to do that, go ahead.

I would like to now ask for suggestions for specific changes to the labeling. The labeling is in the back. I have three sections, the labeling for the physician, for the patient and I don't know what the third one is.

Things that were brought up include --

DR. GRIMMETT: Dr. Sugar, I wrote them all down as each doctor made recommendations. So, even though they are not voted on yet, I did keep a record of that.

DR. SUGAR: Why don't you just go through those and then we can discuss them one by one.

DR. GRIMMETT: Mike Grimmett. Jan Jurkus initially suggested that a looser fit may not be best. I hope I summarized that correctly. Did anyone else have concerns in the labeling that we should address the issue of making this particular

lens tighter in select patients?

DR. SUGAR: Why don't we deal with these one at a time, then. So, Janice is suggesting that the specific fitting recommendations be made in the practitioner labeling that discuss the issue of the fact that this lens may be appropriately fit differently than standard lenses.

DR. GRIMMETT: Due to the discomfort, I assume, that was experienced with this lens.

DR. JURKUS: Right.

DR. SUGAR: Is there a sense that this would be an appropriate addition to the labeling?

DR. EDRINGTON: Dr. Edrington. I would probably stay away from that, telling the practitioner, in a sense, to go tighter on the fit. I think they will, either by word of mouth or at meetings, whatever, determine that or by patients' symptoms of discomfort.

I think if you erred so that they were fitting them too tight and went to the steeper base curve as their default system that, perhaps, other complications that we are not currently aware of could occur.

DR. SUGAR: Other comments on that? Dr. McMahon?

DR. McMAHON: Tim McMahon. This trial was done with one base curve and all the patients are basically forced into one particular lens shape. The sponsor has recognized that they need a different base curve and the data that we are presented did not give us the opportunity to determine whether an alternative base curve would have had some influence on those things.

So I agree with Dr. Edrington, we should probably stay away from it.

DR. SUGAR: There are statements in the practitioner guide that talk about how you measure the fit and the push-up test and that kind of thing. So you are suggesting that something different be added.

DR. JURKUS: Jan Jurkus, again. What I am suggesting is that a statement regarding the patient response of, "The lens doesn't feel right," or some discomfort be, in some way, highlighted because of the fact that the lens may look perfect on the eye where the sponsor said that it may all look okay but if the patient says that it is initially not comfortable, that you might want to go to the steeper design wear. Patient symptomatology plays an important part in the